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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,893	MCCORMICK ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,42,44-50 and 54-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-42, 44-50 and 54-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-40, 43 and 51-53 have been cancelled.

Claims 41 and 48 have been amended.

Claims 58-63 have been added.

2. Claims 41-42, 44-50 and 54-63 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

5. The objection to the first line of the specification for not containing a priority statement is withdrawn in view of the amendments to the specification filed 11/26/2004.

6. The rejections of claims 41-50 and 54-57, parts a, c and d only, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's arguments and the amendments to the claims.

7. The provisional rejection of claims 41-50 and 54-57 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-50 of copending Application No. 10/067,790 in view of Tang et al is withdrawn in view of the amendments to the claims and in view of new grounds of rejection set forth below (see item no. 21 below).

Response to Arguments

8. The rejection of claims 41-42, 44-50, 54-57 and applied to newly added claims 58-63 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

With respect to part b of the rejection under 35 U.S.C. 112, second paragraph, the response filed 11/26/2004 has been carefully considered, but is deemed not to be persuasive. The response states that as presently amended, the claims are not indefinite as the minimal "part" is defined by feature (a) of claim 41. In response to this argument, feature (a) of claim 41 does not particularly point out and distinctly claim which particular surface immunoglobulin epitope or epitopes are contemplated by the phrase and there can be many such epitopes. Claim 41 as written encompasses a polypeptide self-antigen that is encoded at least in part by a nucleic acid in the cells of a B-cell lymphoma, wherein the polypeptide includes a surface immunoglobulin epitope or epitopes. Thus, the claims encompass a polypeptide self-antigen, which comprises an unidentified epitope or epitopes of a surface immunoglobulin and wherein unidentified parts of the polypeptide self-antigen are encoded in part by a nucleic acid in the cells of a B-cell lymphoma. It remains unclear what part or parts of the polypeptide self-antigen are encoded by a nucleic acid in the B-cell lymphoma cells and what other nucleic acid is used to encode the rest of the polypeptide. The epitope or epitopes of a surface immunoglobulin include any fragments of the surface immunoglobulin, the fragments could be part of the constant region, part of the variable domain or domains or part of a

CDR or CDRs or part of a framework or frameworks and any combinations thereof and the claim does not require that the nucleic acid from the B-cell lymphomas actually encode the epitope or epitopes referred to in part (a). Thus, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

9. The rejection of claims 41-42, 44-50, 54-57 and applied to newly added claims 58-63 under 35 U.S.C. 112, first paragraph because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims is maintained (item no. 8 of the previous Office Action mailed 8/25/2004).

The response filed 11/26/2004 has been carefully considered, but is deemed not to be persuasive. The response states that the claims have been amended to recite that the polypeptide self-antigen contains an epitope from a B-cell lymphoma and may be used for B-cell lymphoma patients. Further, the response states that applicant has taken exception to the following statement made by the examiner "Thus, applicant is not enabled for any vaccine composition" and the response acknowledges that the literature shows many failed attempts at cancer vaccines, but notes that several compositions have shown positive results. In response, the literature showing both success and failures is evidence that exemplifies the high degree of unpredictability in the art with respect to cancer therapy and ultimately, which cancer therapies can be predictably practiced with a reasonable expectation of success. It is noted that the instant claims are drawn to a B-cell lymphoma tumor specific "vaccine", which broadly encompasses

preventing a B-cell lymphoma in subjects that do not yet have cancer, as well as completely curing cancer and preventing relapse. While the publication provided by applicant shows some positive results from Phase I clinical trials of 16 patients with B-cell lymphoma, the data provided does not rise to the level of prevention as defined by the claim language. There is no teaching in the prior or post-filing art or in applicant's specification indicating that B-cell lymphomas can be prevented or cured, thus indicating the high degree of unpredictability of preventing and curing cancer. In fact, a "vaccine" would encompass all of the problems associated with treating cancer, as well as additional obstacles such as preventing the events that lead to transformation of a normal cell into a cancerous cell including preventing genetic mutation, and immortalization. Thus, contrary to applicant's assertion, the instant specification does not enable such a "vaccine" for B-cell lymphomas. Amending the claims to recite that the composition is a "therapeutic composition" or similar language would obviate this rejection.

10. The rejection of claims 41-42, 44, 46-50, 54-57 and applied to newly added claims 58-63 under 35 U.S.C. 112, first paragraph because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims is maintained (item no. 9 of the previous Office Action mailed 8/25/2004).

The response filed 11/26/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that while applicant's agree that the three-

dimensional structure of the polypeptide antigen is probably important, the full set of CDRs may not be the critical feature. The response states that the critical feature is the linker and when the linker is changed the VL and VH are arranged differently and induce a different immune response with many linkers rendering the molecule completely useless as a vaccine. The response continues by arguing that Benvenuti et al does not even consider the importance of the linker and Benvenuti et al does not indicate how many CDRs and what type are needed. In response to these arguments, while it appears that the linker is one critical feature of applicant's invention, complete VH and VL domains are also required. Applicant's claims still broadly encompass a polypeptide self-antigen that includes an epitope or epitopes of a surface immunoglubulin. Thus, applicant's base claim encompasses using any epitope(s) from the constant region or the hinge or the frameworks or the CDRs, which would not produce a conformationally-dependent idiotype that mimics the natural surface Ig expressed on B-cell lymphomas. Further, the claims encompass an idiotypic eptiope of only part of the VH and only part of the VL domains, which encompasses incomplete VH and VL domains that do not contain the full complement of 6 CDRs, from both the heavy chain and light chain and would not mimic the idiotype expressed on B-cell lymphomas. Applicant has not provided any objective evidence that epitopes from the constant regions or hinge region or frameworks, or from only part of the VH and VL domains of B-cell lymphoma surface immunoglobulins produce conformational-dependent epitopes (idiotypes) mimicking the surface immunoglobulins expressed on B cell lymphomas, which are complete immunoglobulins (i.e., comprise complete variable

light and heavy chains as well as complete heavy and light constant regions). Further, applicant has not provided objective evidence that incomplete VH and VL scFvs connected via applicants linkers predictably reproduce idiotypes that mimic the natural surface Ig expressed in B-cell lymphomas. Applicant acknowledges that the three-dimensional structure of the polypeptide self-antigen is probably important and as evidenced by applicant's own specification at page 45, lines 16-19, which states that the conformation of the relevant epitopes (idiotypes) in solution should resemble or mimic the same epitopes of the native protein as they appear on the surface of the tumor cell and at page 16 of the specification indicates that an idiotype is formed by the association of the hypervariable or complementary determining regions of VH and VL domains. One of skill in the art could not predictably use epitopes derived from any part of the surface immunoglobulin or epitopes that do not contain complete VH and VL domains, which are incomplete structures to mimic the idiotypes of native surface immunoglobulins expressed in B-cell lymphomas. In fact, as evidenced by Casper et al (previously cited on PTO-892 mailed 8/25/2004), "a change of one or two amino acids in the second complementarity-determining region (CDR2) of the heavy chain seemed to be responsible for the loss of binding to the treatment of MoAb." (anti-idiotypic antibody) (see page 3699, left column). Thus, Casper et al teach that even minor structural changes (i.e., one or two amino acids) in a single CDR result in a structural change such that the idiotype of the surface Ig no longer resembles the original surface Ig expressed on B-cell lymphomas. Further, as pointed out by applicant Benvenuti et al makes clear that the immune response (i.e., induction of anti-idiotypic antibodies) is

directed exclusively against conformationally combined VL/VH determinants (see page 1557, right column), which further evidences that the conformationally combined VH/VL pairs are required to mimic the natural idiotype of the surface immunoglobulin expressed in B-cell lymphomas. With respect to applicants arguments that Benevenuti et al immunize with naked DNA whereas the instant claims immunize with a polypeptide self-antigen, Benevenuti et al teach that anti-idiotypic antibodies are produced and directed exclusively against combined VH/VL determinants (i.e., idiotypes), which evidences that (a) the polypeptide is expressed and (b) the determinant or epitope (i.e., idiotype) is formed by the association of complete VH/VL pairs.

It is reiterated that applicant is enabled for a polypeptide self-antigen comprising both VH and VL domains, wherein the heavy and light chain CDRs are in their proper order and in the context of framework sequences, which maintain their required conformation and therefore, mimic the natural idiotype expressed on the surface of B-cell lymphomas.

11. The rejection of claims 41-42, 44-47, 54 and applied to newly added claims 61-62 under 35 U.S.C. 102(b) as being anticipated by Casper et al is maintained.

The response filed 11/26/2004 has been carefully considered, but is deemed not to be persuasive. The response argues the scFv of Casper et al is a fusion protein comprising GM-CSF. In response to this argument and as stated in the previous office action at page 16, applicant's claimed polypeptide self-antigen "includes...", which is equivalent to "comprising" and is inclusive or open-ended and does not exclude

additional unrecited elements (see MPEP 2111.03). Therefore, the scFv-GM-CSF taught by Casper et al reads on the claims. The response also argues that there is no assurance that the polypeptide is correctly folded or that the specific antigenic epitope is maintained and the data in figure 2 suggests that the GM-CSF protein portion fused to the scFv protein fused to the scFv is detrimental and the response speculates that the most likely reason being interfering with protein folding or blocking of the epitope. Applicant concludes that that the polypeptide-self antigen is not "in correctly folded form" as recited in claim 1, feature (c). Casper et al teach a scFv-GM-CSF idiotype protein that induces an immune response, in fact, a significant and specific anti-Id immune response as shown in Figures 2 and 3, indicating that the scFv-GM-CSF is correctly folded, thereby mimicking the idiotype expressed by the natural surface Ig expressed in B-cell lymphomas. See also the text at page 3702, where Casper et al states "All mice developed a specific anti-Id immune response after vaccination".

Applicant also argues that claim 1, feature (d), indicates that the polypeptide "is capable of inducing an immune response in a mammal...without the need for adjuvant or other immunostimulatory materials" and the polypeptide taught by Casper contains a well-known material for enhancing the immune response. The phrase "capable of" is non-limiting because an element "capable of" performing a function is not a positive limitation, but only requires the ability to so perform. In view of the evidence of Casper et al, which shows that a scFv (adenovirus), which expressed a scFv polypeptide that was not conjugated to another polypeptide and was identical to the scFv (2A12) of the scFv-GM-CSF fusion, was capable of inducing an immune response as shown in

Figures 2 and 3. Thus, as a property is inherent to a product the scFv of Casper et al in the absence of adjuvant or other immunostimulatory materials would necessarily be capable of inducing an immune response without the need for adjuvant or other immunostimulatory materials absent objective evidence to the contrary. With respect to newly added claims 61-62, as discussed above Capser et al teach a scFv-GM-CSF fusion protein which is a composition further comprising an immunostimulatory cytokine and as admitted by applicant at page 11 of the response Casper et al teach a polypeptide antigen (idiotype) conjugated to KLH, a well-known adjuvant (i.e., idiotype-KLH).

Applicant's arguments with respect to newly added claims 59-60 and the production of the polypeptide self-antigen in plant cells is acknowledged, however, these claims are not included in the instant rejection and not relevant.

12. The rejection of claims 41-42, 44-47 and applied to newly added claims 58, 61-63 under 35 U.S.C. 102(b) as being anticipated by Hawkins et al is maintained.

The response filed 11/26/2004 has been carefully considered, but is deemed not to be persuasive. The response argues as above for Casper et al that there is no indication that the polypeptide is folded correctly or that it is capable of inducing an immune response without an adjuvant or immunostimulatory agent and the approach of using DNA vaccines lacks any suggestion of a correctly folded protein being produced because the scFv nucleic acid construct is artificial. In response to these arguments and as pointed out in the previous Office action, Hawkins et al teach administration of

the scFv polypeptide not conjugated to another polypeptide generated a polyclonal anti-idiotypic antibody response, clearly indicating that the scFv was in correctly folded form and mimicked the natural surface Ig expressed in B-cell lymphomas (see pages 20-21).

It is noted that newly added claims 58 and 61-63 recite wherein the polypeptide is not conjugated to another polypeptide, which was addressed above and the composition further comprises an adjuvant and further comprises an immunostimulatory cytokine or chemokine selected from IL-1, IL-2, IL-12, IL-18 and IFN-gamma. Hawkins et al teach that IFN-gamma could be administered separately (see page 28).

13. The rejection of claims 41-42, 44-50, 54-57 and applied to newly added claims 61-62 under 35 U.S.C. 103(a) as being unpatentable over Casper et al in view of Tang et al and Hsu et al is maintained.

The response filed 11/26/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that all the arguments above regarding the deficiencies of Casper et al apply here as well and none of the secondary references compensate for the basic difference of not teaching a correctly folded polypeptide or a polypeptide capable of eliciting an immune response without an adjuvant or immunostimulatory agent. In response, the arguments presented above (see Casper et al) by the examiner apply here as well in that Casper et al teach that the scFv-GM-CSF elicits an anti-idiotype antibody immune response, which evidences that the polypeptide is in correctly folded form. Further, the scFv adenovirus construct of Casper et al expresses the scFv (not fused or conjugated to another polypeptide), providing

evidence that the scFv is capable of inducing an immune response in the absence of an adjuvant or immunostimulatory agent.

The response argues the Tang reference stating that the randomization process of Tang et al is performed differently and would produce a different result from applicant's present linker optimization. The response states that the linker of Tang et al is 18 amino acids long, being encoded by $(SNN)_{18}$ and is a truly random linker, whereas claims 55-57 provide for a repeated pattern of degenerate repeated triplet nucleotides with specific nucleotides at certain locations. In response to these arguments instant claim 55 is a linker from a randomized library of linkers that vary in size and sequence and the only requirement in claim 55 is that the trinucleotide does not contain the same nucleotide at all three positions (i.e., TTT) and claim 56 recites that the first two positions of the trinucleotide are selected from dA, dG, dC, dT. Thus, claims 55 and 56 are not limited to specific nucleotides at certain locations nor are they restricted to any particular size and claim 55 recites that the linkers are from a randomized library of linkers. The features upon which applicant relies (i.e., non-random linkers) are not recited in the rejected claims. With respect to claim 57, the triplet (SNN) of Tang et al wherein S is C or G and N is any nucleotide reads on the triplets GCT and GGT encompassed by claim 57.

Applicant also argues that the present invention is different from the prior art in that the present invention is "capable of inducing an immune response...without the need for adjuvant or other immunostimulatory materials", whereas Casper et al and Hsu et al provide strong motivation to use a variety of adjuvants and immunostimulatory

agents and a negative teaching to use an antigen without such enhancers. Applicant is reminded that the phrase "capable of" is non-limiting because an element "capable of" performing a function is not a positive limitation, but only requires the ability to so perform. As discussed above, Casper et al teach that the scFv lacking GM-CSF is capable of inducing an immune response without the need for adjuvant or other immunostimulatory materials (see Figures 2 and 3). Additionally, it is pointed out that newly added claims 61-63 recite that the composition further comprises an adjuvant or other immunostimulatory agents, contrary to applicant's arguments.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

14. The rejection of claims 41-42, 44-50, 54-57 and applied to newly added claims 58, 61-62 under 35 U.S.C. 103(a) as being unpatentable over Hawkins et al in view of Tang et al and Hsu et al is maintained.

The response filed 11/26/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that all of the comments above regarding the deficiencies of Hawkins et al, Tang et al and Hsu et al apply here as well and Hawkins has the same deficiencies as above for Casper et al and a few others. In response, the arguments above by the examiner with respect to Hawkins et al, Tang et al and Hsu et

al apply here as well. Applicant has not argued the asserted additional deficiencies with respect to Hawkins et al of the instant rejection.

New Grounds of Objections/Rejections

15. The amendment to the first line of the specification filed 11/26/2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment claims priority to Application No. 60/155,979, filed on September 24, 1999, and incorporates the disclosure in its entirety by reference. The priority application cannot be incorporated by reference after the original filing of the instant application. This objection can be overcome by removing the incorporation by reference statement, thereby removing the new matter introduced therein.

See United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application" (see Part VII).

Applicant is required to cancel the new matter in the reply to this Office Action

16. Claims 41-42, 44-50, 54-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite for reciting "a nucleic acid encoding a peptide sequence overlapping a peptide sequence encoded by said nucleic acid in the cells of said tumor"

in claim 41. It is totally unclear what peptide is encoded by the nucleic acid. Does the nucleic acid encode a peptide that shares only some sequence overlap with the encoded peptide in the cells of the tumor? What does the rest of the nucleic acid encode, some other protein not encoded in the tumor cells?

Claim 41 recites the limitation "said nucleic acid". There is insufficient antecedent basis for this limitation in the claim. Claim 41 recites a nucleic acid that encodes, in part, a polypeptide self-antigen as well as a nucleic acid for producing the polypeptide self-antigen that encodes a peptide sequence that overlaps a peptide sequence of the polypeptide self-antigen expressed in tumor cells. Is the nucleic acid encoding the polypeptide self-antigen expressed in tumor cells or is the nucleic acid the nucleic acid transformed or transfected in a cell or organism for producing the encoded polypeptide and do the two nucleic acids encode the same protein or just an overlapping peptide sequence?

17. Claim 58 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The response filed 11/26/2004 has introduced NEW MATTER into the claims. Newly added claim 58 recites that the polypeptide self-antigen of base claim 41 is not fused or conjugated to another polypeptide. The response did not point out where

support for newly added claim 58 could be found in the originally filed disclosure. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP 714.02 and 2163.06 ("Applicant should therefore specifically point out the support for any amendments made to the disclosure."). Instant claim 58 now recites limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in newly added claim 59, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in present claim 59 in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action.

18. Claims 41-41, 44-50 and 54-63 are rejected under 35 U.S.C.103(a) as being unpatentable over Caspar et al (Blood, 90(9):3699-3706, November 1997, cited on PTO-892 in the previous office action mailed 8/25/2004) in view of Tang et al (Journal of Biological Chemistry, 271(26):15682-15686, June 1996, cited on PTO-892 in the previous office action mailed 8/25/2004) and Fiedler et al (Immunotechnology, 3(3):205-216, October 1997, Ids filed 3/8/04) and Hakim et al (Journal of Immunology,

157:5503-5511, 1996, Ids filed 1/10/05) and Hsu et al (Blood 89(9):3129-3135 1 May 1997, cited on PTO-892 in the previous office action mailed 8/25/2004).

The claims have been described supra.

Claims 59-60 recite that the polypeptide self-antigen is produced in plant cells and claim 63 further limits the immunostimulatory cytokine reciting that it is selected from the groups consisting of IL-1, IL-2, IL-12, IL-18 and IFN-gamma.

Caspar et al has been described supra. Caspar et al does not specifically teach the scFv in unit dosage form in aqueous solution at a concentration between about 0.1 and 10 mg/ml or administration to a human subject or a randomized library of linkers with the instantly claimed criteria or the production of the polypeptide self-antigen in plant cells and wherein the cytokine is IL-1, IL-2, IL12, IL-18 or IFN-gamma. These deficiencies are made up for in the teachings of Tang et al and Fiedler et al and Hakim et al and Hsu et al.

Tang et al teach that a linker suitable for one scFv will not be optimal for other scFvs and linker length and sequence affect the expression level, solubility, stability and binding affinity of the scFvs (see page 15682, right column). Tang et al teach a method of selecting active scFvs synthesized form libraries of scFv genes with randomized linker DNA sequences (see abstract and pages 15682-15684).

Fiedler et al teach that scFv can be made in high quantities in transgenic plant cells, wherein 4-6% to 3-4% of the total protein found in leaves and seed, respectively, can be recombinantly expressed scFv. Furthermore, Fiedler et al teach that such recombinant scFv is functionally active.

Hakim et al teach immunotherapeutic compositions comprising a scFv constructed from the Ig variable regions from B cell lymphomas (i.e., idiotype) for inducing a polyclonal anti-idiotype response (see entire document). Hakim et al teach that the scFv needed to be conjugated to a strong carrier such as keyhole limpet hemocyanin (KLH) and mixed with an adjuvant to induce a tumor-protective anti-idiotypic response (see page 5503, left column). Hakim et al also teaches that scFv-IL-2 and scFv-IFN-gamma as well as others enhanced the immunogenicity of the idiotype and elicited and anti-idiotype response that was protective against tumor challenge (see page 5503, right column).

Hsu et al teach clinical trials in which patients with B cell lymphoma receiving subcutaneous immunization of 0.5 mg of B cell lymphoma immunoglobulin induced specific immune responses (humoral) against the immunoglobulin (anti-idiotype immune responses) expressed by their own B cell lymphomas and the ability to make such an immune response is correlated with a more favorable clinical outcome (see abstract, page 3130, right column, page 3131, right column). Hsu et al teach "The FFP [freedom from disease progression] and survival of those patients mounting an antitumor Id immune response is significantly longer compared to those who did not develop an immune response or to that of nonvaccinated, historical controls".

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a method of inducing an immune response in subjects having B-cell lymphoma comprising administering a scFv comprising B-cell lymphoma Ig epitopes for therapeutic benefit of B cell lymphomas as

taught by Caspar et al, wherein the scFv comprises VH and VL domains linked by a randomized linker as taught by Tang et al and to combine the scFv with an adjuvant or IL-2 or IFN-gamma to enhance the immunogenicity of the scFv (idiotype) and elicit an anti-scFv (anti-idiotype) response as taught by Hakim et al and to have produced the scFv in a plant as taught by Fiedler et al. One of skill in the art would have been motivated to produce the polypeptide self-antigen in plant cells because Fiedler et al teach plant expression of scFvs eliminates the need for complex culture media, sterility or large culture vessels, possibility of composting plant waste material and no contamination with mammalian viruses or bacterial endotoxins, the latter two are especially important for producing scFvs for therapeutic use and one of ordinary skill in the art would have had a reasonable expectation of success because Fiedler et al teach the expression of a functional scFv in plants. Further, one of ordinary skill in the art would have been motivated to produce a method of inducing an immune response in subjects having B-cell lymphoma comprising administering a scFv comprising B-cell lymphoma Ig epitopes because Hsu et al teach clinical trials in which patients with B cell lymphoma receiving subcutaneous immunization of 0.5 mg of B cell lymphoma immunoglobulin induced specific immune responses against the immunoglobulin (anti-idiotype immune response) expressed by their own B cell lymphomas and the ability to make such an immune response is correlated with a more favorable clinical outcome. In addition, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have optimized the scFv linker because Tang et al teach that a linker suitable for one scFv will not be optimal for other scFvs and linker length and

sequence affect the expression level, solubility, stability and binding affinity of the scFvs and to use the scFv with an adjuvant or as a scFv-IL-2 or scFv-IFN-gamma fusion protein to enhance the immunogenicity of the scFv and elicit an anti-scFv response (anti-idiotype response) that would be protective against tumor challenge as taught by Hakim et al and the skilled artisan would have been motivated to optimize the dosages and administration of the scFv for optimum therapeutic benefit of B cell lymphomas. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a method of inducing an immune response in B-cell lymphoma patients comprising administering a composition comprising a scFv comprising B-cell lymphoma Ig epitopes for therapeutic benefit of B cell lymphomas as taught by Caspar et al, wherein the scFv comprises VH and VL domains linked by a randomized linker as taught by Tang et al and to combine the scFv with an adjuvant or IL-2 or IFN-gamma to enhance the immunogenicity of the scFv (idiotype) and elicit an anti-scFv (anti-idiotype) response that would be protective against tumor challenge as taught by Hakim et al and to have produced the scFv in a plant as taught by Fiedler et al and in view of the teachings of Hsu et al, demonstrating that administration of B-cell lymphoma immunoglobulin to patients with B cell lymphoma induced specific immune responses against the immunoglobulin (anti-idiotype immune response) expressed by

their own B cell lymphomas and the ability to make such an immune response is correlated with a more favorable clinical outcome.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

19. Claims 41-41, 44-50 and 54-63 are rejected under 35 U.S.C.103(a) as being unpatentable over Hawkins et al (Blood, 90(9):3699-3706, November 1997, cited on PTO-892 in the previous office action mailed 8/25/2004) in view of Tang et al (Journal of Biological Chemistry, 271(26):15682-15686, June 1996, cited on PTO-892 in the previous office action mailed 8/25/2004) and Fiedler et al (Immunotechnology, 3(3):205-216, October 1997, Ids filed 3/8/04) and Hakim et al (Journal of Immunology, 157:5503-5511, 1996, Ids filed 1/10/05) and Hsu et al (Blood 89(9):3129-3135 1 May 1997, cited on PTO-892 in the previous office action mailed 8/25/2004).

The claims have been described supra.

Hawkins et al teach a method of inducing a B cell lymphoma-specific immune antibody response in a subject comprising administering a scFv that includes the VH and VL domains (i.e., at least part of the VH and VL domains), wherein the VH and VL domains are from immunoglobulins expressed on B cell lymphomas (i.e., epitopes unique to the tumor cells) (see entire document, particularly pages 2-8 and 19-20). Thus, the scFv includes an epitope that is unique to B cell lymphoma cells, includes the VH and VL domains, which are at least part of the VH and part of the VL, respectively. Hawkins et al teach the scFv in PBS (i.e., a pharmaceutically acceptable carrier or

excipient) administered to subject by subcutaneous immunization (parenteral route) at 12.5 μg three times about two weeks apart (see page 19). Hawkins et al teach that administration of the scFv generated a polyclonal anti-idiotypic antibody response, which was detected by testing the sera of the host by ELISA (enzyme immunoassay) and flow cytometry (FACS analysis) (see pages 7 and 20-21). Hawkins et al do not specifically teach the scFv in unit dosage form in aqueous solution at a concentration between about 0.1 and 10 mg/ml or administration to a human subject or an amino acid linker that has between one and about 50 residues, consists of between one and twelve different amino acids and facilitates secretion and correct folding of the scFv to mimic the tumor epitope in its native form on the tumor cells or a randomized library of linkers or the production of the polypeptide self-antigen in plant cells and wherein the cytokine is IL-1, IL-2, IL12, IL-18 or IFN-gamma with the instantly claimed criteria. These deficiencies are made up for in the teachings of Tang et al and Fiedler et al and Hakim et al and Hsu et al

Tang et al have been described supra.

Fiedler et al have been described supra.

Hakim et al have been described supra.

Hsu et al have been described supra.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a method of inducing an immune response in subjects having B-cell lymphoma comprising administering a scFv comprising B-cell lymphoma Ig epitopes for therapeutic benefit of B cell lymphomas as

taught by Hawkins et al, wherein the scFv comprises VH and VL domains linked by a randomized linker as taught by Tang et al and to combine the scFv with an adjuvant or IL-2 or IFN-gamma to enhance the immunogenicity of the scFv (idiotype) and elicit an anti-scFv (anti-idiotype) response as taught by Hakim et al and to have produced the scFv in a plant as taught by Fiedler et al. One of skill in the art would have been motivated to produce the polypeptide self-antigen in plant cells because Fiedler et al teach plant expression of scFvs eliminates the need for complex culture media, sterility or large culture vessels, possibility of composting plant waste material and no contamination with mammalian viruses or bacterial endotoxins, the latter two are especially important for producing scFvs for therapeutic use and one of ordinary skill in the art would have had a reasonable expectation of success because Fiedler et al teach the expression of a functional scFv in plants. Further, one of ordinary skill in the art would have been motivated to produce a method of inducing an immune response in subjects having B-cell lymphoma comprising administering a scFv comprising B-cell lymphoma Ig epitopes because Hsu et al teach clinical trials in which patients with B cell lymphoma receiving subcutaneous immunization of 0.5 mg of B cell lymphoma immunoglobulin induced specific immune responses against the immunoglobulin (anti-idiotype immune response) expressed by their own B cell lymphomas and the ability to make such an immune response is correlated with a more favorable clinical outcome. In addition, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have optimized the scFv linker because Tang et al teach that a linker suitable for one scFv will not be optimal for other scFvs and linker length and

sequence affect the expression level, solubility, stability and binding affinity of the scFvs and to use the scFv with an adjuvant or as a scFv-IL-2 or scFv-IFN-gamma fusion protein to enhance the immunogenicity of the scFv and elicit an anti-scFv response (anti-idiotype response) that would be protective against tumor challenge as taught by Hakim et al and the skilled artisan would have been motivated to optimize the dosages and administration of the scFv for optimum therapeutic benefit of B cell lymphomas. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a method of inducing an immune response in B-cell lymphoma patients comprising administering a composition comprising a scFv comprising B-cell lymphoma Ig epitopes for therapeutic benefit of B cell lymphomas as taught by Hawkins et al, wherein the scFv comprises VH and VL domains linked by a randomized linker as taught by Tang et al and to combine the scFv with an adjuvant or IL-2 or IFN-gamma to enhance the immunogenicity of the scFv (idiotype) and elicit an anti-scFv (anti-idiotype) response that would be protective against tumor challenge as taught by Hakim et al and to have produced the scFv in a plant as taught by Fiedler et al and in view of the teachings of Hsu et al, demonstrating that administration of B-cell lymphoma immunoglobulins to patients with B cell lymphoma induced specific immune responses against the immunoglobulin (anti-idiotype immune response) expressed by

their own B cell lymphomas and the ability to make such an immune response is correlated with a more favorable clinical outcome.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 41-42, 44-50 and 54-63 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-50 of copending Application No. 10/067,790 in view of Hawkins et al (WO 94/08008, 4/14/1994, cited on PTO-892 in the previous office action mailed 8/25/2004) and Hakim et al (Journal of Immunology, 157:5503-5511, 1996, Ids filed 1/10/05).

The instant claims are drawn to a method of inducing an immune response in B-cell lymphoma patients comprising administering a composition comprising a polypeptide self-antigen and a pharmaceutically acceptable carrier useful as a B-cell lymphoma tumor specific vaccine in a subject with a tumor, wherein the polypeptide

self-antigen: (1) includes a surface immunoglobulin (surface Ig) epitope or epitopes unique to or over expressed by the tumor cells, (2) is produced in a cell or organism transformed by the nucleic acid, (3) is obtained from the transformed cell or organism in correctly folded form, and (4) the polypeptide self-antigen is capable of inducing an immune response in a mammal without the need for adjuvant or other immunostimulatory materials. Further, the polypeptide self-antigen is not to be fused or conjugated to another polypeptide (claim 58) and is produced in plant cells and is a scFv that includes at least part of the VH and VL domains, wherein the VH and VL domains are linked by an amino acid linker between 1 and about 50 residues and facilitates the secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on said tumor cell or the linker connecting the VH and VL domains is a member of a randomized library of linkers with the following requirements: position 1 cannot be the same nucleotide as position 2 of a repeated triplet, position 2 cannot be the same nucleotide as position 3 of a repeated triplet, and position 1 cannot be the same nucleotide as position 3 of a repeated triplet (claim 55), wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of dA, dG, dC or dT (claim 56) and wherein the linker at position 1 is dA or dG, position 2 is dC or dG, and position 3 is dT (claim 57). The polypeptide self-antigen is administered by a parenternal route, including subcutaneous, transdermal or intramuscular and the composition is in unit dosage form in aqueous solution at a concentration between about 0.1 and about 10 mg/ml and the subject is a human. Further, the polypeptide self-antigen further comprises an adjuvant, a, cytokine or a

chemokine, wherein the cytokine is selected from the group consisting of IL-1, IL-2, IL-12, IL-18 and IFN-γ.

Claims 41-50 of copending Application No. 10/067,790 is drawn to a method of inducing a tumor-specific immune response in a tumor-bearing subject comprising administering a vaccine composition comprising polypeptide self-antigen and a pharmaceutically acceptable in a subject with a tumor, wherein the polypeptide self-antigen: (1) includes a surface immunoglobulin (surface Ig) epitope or epitopes unique to or over expressed by the tumor cells, (2) is produced in a cell or organism transformed by the nucleic acid, (3) is obtained from the transformed cell or organism in correctly folded form, and (4) the polypeptide self-antigen is capable of inducing an immune response in a mammal without the need for adjuvant or other immunostimulatory materials. Further, the polypeptide self-antigen is produced in plant cells and is a scFv that includes at least part of the VH and VL domains, wherein the VH and VL domains are linked by an amino acid linker between 1 and about 50 residues and facilitates the secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on said tumor cell or the linker connecting the VH and VL domains is a member of a randomized library of linkers with the following requirements: position 1 cannot be the same nucleotide as position 2 of a repeated triplet, position 2 cannot be the same nucleotide as position 3 of a repeated triplet, and position 1 cannot be the same nucleotide as position 3 of a repeated triplet, wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of dA, dG, dC or dT (claim 56) and wherein the linker at position 1 is dA or dG, position 2 is dC or

dG, and position 3 is dT (claim 57). The polypeptide self-antigen is administered by a parenternal route, including subcutaneous, transdermal or intramuscular and the composition is in unit dosage form in aqueous solution at a concentration between about 0.1 and about 10 mg/ml and the subject is a human. The claims in copending Application No. 10/067,790 do not specifically teach that the polypeptide self-antigen is not conjugated to another polypeptide or wherein the composition further comprises an adjuvant or an immunostimulatory cytokine or chemokine selected from IL-1, IL-2, IL-12, IL-18 and IFN-γ. This deficiency is made up for in the teachings of Hawkins et al and Hakim et al.

Hawkins et al have been described supra.

Hakim et al has been described supra.

The claims in the instant application are obvious variants of copending Application No. 10/067,790 because it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of inducing an immune response in a B-cell lymphomas patient comprising administering a composition comprising a polypeptide self-antigen that includes epitopes of a surface immunoglobulin (i.e., idiotypes), wherein the polypeptides self-antigen is not conjugated to another polypeptide as taught by Hawkins et al or further comprises an adjuvant or immunostimulatory cytokine as taught by Hakim et al for therapeutic benefit of B cell lymphomas.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of inducing an immune

response in a B-cell lymphomas patient comprising administering a composition comprising a polypeptide self-antigen that includes epitopes of a surface immunoglobulin (i.e., idiotypes), wherein the polypeptides self-antigen is not conjugated to another polypeptide as taught by Hawkins et al or further comprises an adjuvant or immunostimulatory cytokine as taught by Hakim et al because Hakim et al teach an adjuvant or IL-2 or IFN-gamma enhances the immunogenicity of the scFv (idiotype) and elicits an anti-scFv (anti-idiotype) response that would be protective against tumor challenge.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

22. No claim is allowed.

23. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER